CHAPTER 1

INTRODUCTION

CONTROLLED DRUG DELIVERY

The pharmaceutical industry over the past decades has been facing tough challenges in brining (NCEs) to market for prevention and treatment of existing and newer diseases. Furthermore, the cost of developing NCEs is continually rising, and today it costs around US $ 1 billion to bring one NCE to market (Schmid and Smith, 2005). There is, however, a valuable role being played by drug delivery system in providing optimized products for existing drugs in terms of either enhanced or improved presentation of the drug to the systemic circulation.

The earliest studies in the field of controlled drug delivery date back to the 1950s. Since then, a large number of drug products with controlled release characteristics, have been introduced. The incredible growth can be attributed to several advantages that these products offer, including improved patient compliance, better therapeutic efficiency, potential for cost saving, patentability and opportunity for extending product life-cycle. Various technologies have been investigated in order to achieve different kinds of modified release, e.g. sustained, delayed, pulsatile, targeted and programmed release. Regardless of the delivery type, the main mechanisms associated with drug transport in these systems include diffusion, swelling, erosion, ion exchange, and osmotic effect (Theeuwes, 1975; Korsmeyer et al., 1983; Khurahashi et al., 1996; Colombo et al., 1999; Bettini et al., 2001; Narasimhan, 2001; Durig and Fassihi, 1999, 2002; Sako et al., 2002; Turner et al., 2004).

BENEFITS OF CONTROLLED RELEASE DRUG DELIVERY SYSTEMS

By improving the way in which drugs are delivered, a controlled release drug delivery system is capable of achieving the following benefits (Robinson, 1987)

- Maintenance of optimum therapeutic drug concentration in the blood with minimum fluctuations.
- Predictable and reproducible release rates for extended duration.
- Enhancement of activity duration for short half-life drugs.
- Elimination of frequent dosing, inconvenience of nighttime administration of drug.
- Optimized therapy and better patient compliance.
- Reduction of the incidences and degree of toxic and side effects such as irritation of gastro-intestinal tract caused by some orally administrated drugs.

ORAL CONTROLLED DRUG DELIVERY SYSTEMS

Among the various controlled release (CR) drug delivery systems available in market, oral controlled release systems hold the major market share because of their obvious advantages of ease of administration and better patient compliance (Verma et al., 2002). A number of design options are available to control or modulate the drug release from a oral dosage form. Majority of oral CR dosage forms falls in the following categories,

- Matrix systems
- Reservoir systems and
- Osmotic systems.

In matrix systems, the drug is embedded in a polymer matrix and the release takes place by partitioning of drug into the polymer matrix and the release medium. In contrast, reservoir systems have a drug core surrounded/ coated by a rate controlling membrane. However, factors like pH, presence of food, and other physiological factors may affect drug release from conventional CR systems (matrix and reservoir). Osmotic systems utilize the principles of osmotic pressure for the delivery of drugs. Drug release from these systems is independent of pH and other physiological parameters to a large extent and it is possible to modulate the release characteristics by optimizing the properties of drug and system. Osmotic pumps are well known for delivering drug at a zero order rate.

OSMOTIC SYSTEMS

Since pharmaceutical agents can be delivered in a controlled pattern over a long period by osmotic pressure, past two decades have witnessed increasing interest in the development of osmotic systems (Ayer and Theeuwes, 1980; Speers and Bonnano, 1999).

PRINCIPLE OF OSMOSIS

Osmosis is defined as a process in which the solvent molecules pass through a semipermeable membrane from a pure solvent to a solution or from a dilute solution to a concentrated solution. Abbe Nollet first reported osmotic effect in 1748, but Pfeffer pioneered the field by quantitating the osmotic effect. He measured the effect in 1877 by utilizing a membrane, which was selectively permeable to water but impermeable to

sugar (Fig. 1.1) (Santus and Baker, 1995). This membrane separated sugar solution from pure water. Pfeffer observed a flow of water in to the sugar solution that was halted when a pressure (π) was applied to the sugar solution, hence postulated that this pressure, the osmotic pressure (π) of the sugar solution was directly proportional to the solution concentration and absolute temperature.

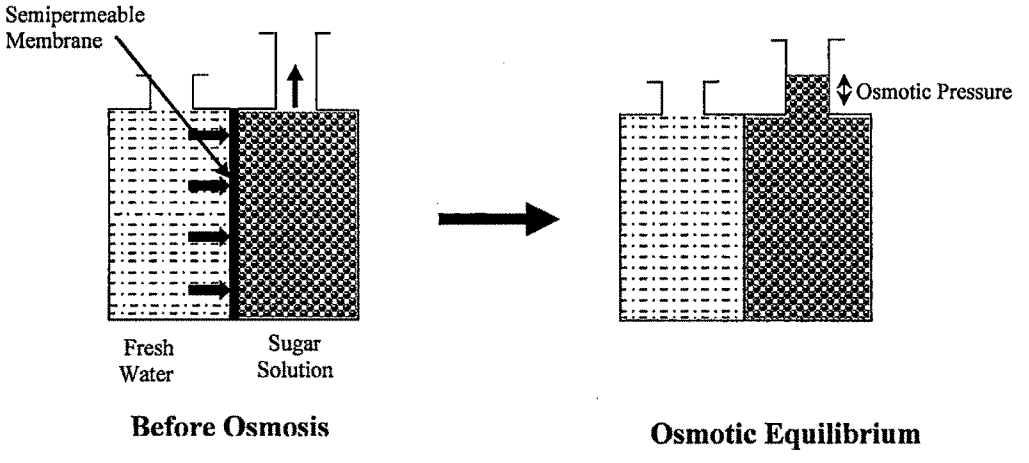

Fig. 1.1 A schematic illustrating osmotic flow and the attainment of osmotic equilibrium

Van't Hoff established the analogy between the Pfeffer results and the ideal gas laws by the expression,

$$\pi V = nRT \qquad (1)$$

Where, π is the osmotic pressure in atm, V is the volume of solutions in liters, n is the number of moles of solutes, R is gas constant equal to 0.082 liter atm/mole, and T is the absolute temperature.

Osmotic pressure can be obtained to a good approximation vapour pressure measurements by using the expression.

$$\pi = RT/V \ln (P_0/P) \qquad (2)$$

Where, P_0 is the vapour pressure of pure solvent, P is the vapour pressure of the solution. V is the molar volume of the solvent.

The osmotic water flow across the membrane is given by,

$$dv/dt = A\theta\Delta\pi/l \qquad (3)$$

Where, dv/dt is the water flow across the membrane area A and thickness l, whose permeability is θ. Δπ is the osmotic pressure difference between the two solutions on either side of the membrane.

Osmosis is the phenomenon that makes controlled drug delivery a reality. Osmotic pressure created due to imbibition of fluid from external environment regulates the delivery of drug from the osmotic device. There are various factors that govern a particular pattern of drug delivery like nature of semipermeable membrane, diameter of delivery orifice, surface area of semipermeable membrane, nature and concentration of osmogen etc. (Verma et al., 2002)

Pharmaceutical solutes used in osmotic pumps and the osmotic pressures of these saturated solutions are presented in Table 1.1 (Wong et al., 1986).

Table 1.1 : Osmotic Pressures of Saturated Solutions of Commonly Used Pharmaceutical Solutes

Compound or Mixture	Osmotic pressure (atm)	Compound or Mixture*	Osmotic pressure (atm)
Sodium chloride	356	Lactose- fructose	500
Fructose	355	Dextrose- fructose	450
Potassium chloride	245	Sucrose- fructose	430
Sucrose	150	Mannitol- fructose	415
Dextrose	82	Lactose- sucrose	250
Potassium sulphate	39	Lactose- dextrose	225
Mannitol	138	Mannitol- dextrose	225
Sodium phosphate tribasic	36	Dextrose- sucrose	190
Sodium phosphate dibasic	31	Mannitol- sucrose	170
Sodium phosphate monobasic	28	Mannitol- lactose	130

* 50: 50

ADVANTAGES OF OSMOTIC DRUG DELIVERY

Osmotic drug delivery systems for oral and parenteral use offer distinct and practical advantages over other means of delivery. The following advantages have contributed to the popularity of osmotic drug delivery systems (Santus and Baker, 1995).

- Desired zero-order delivery rate is achieved with osmotic systems as shown by in vitro and in vivo experiments.
- Delivery may be delayed or pulsed, if desired.
- For oral osmotic systems, drug release is independent of gastric pH and hydrodynamic conditions.
- Higher release rates are possible with osmotic systems compared with conventional diffusion-controlled drug delivery systems.
- The release rate of osmotic systems is highly predictable and can be preprogrammed by modulating the release control parameters.
- A high degree of in vivo-in vitro correlation (IVIVC) is obtained in osmotic system.
- The release from osmotic systems is minimally affected by the presence of food in the gastrointestinal tract (GIT).

OSMOTIC PUMPS

➢ *ELEMENTARY OSMOTIC PUMP (EOP)*

The concept of osmotic delivery through elementary osmotic pump (EOP) was first introduced by Theeuwes (Theeuwes, 1975). The EOP consists of an osmotic core with the drug, surrounded by a semipermeable membrane with a delivery orifice. Fig. 1.2 shows schematic diagram of elementary osmotic pump (EOP), which in its simplest design, consists of an osmotic core (containing drug with or without an osmogent) coated with a semipermeable membrane.

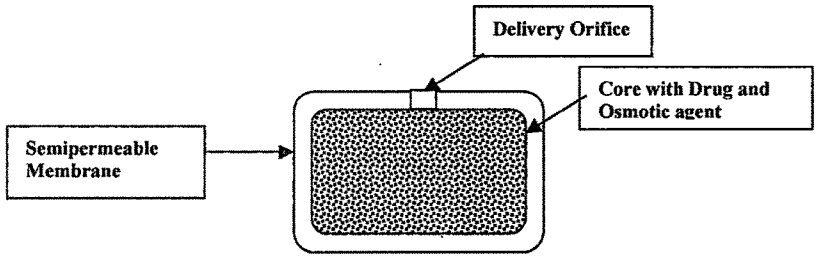

Fig. 1.2 Elementary Osmotic Pump

The device in fact represents a coated tablet with a hole and perhaps represents ultimate simplification of the original Rose-Nelson pump, when this coated tablet is exposed to an aqueous environment, the osmotic pressure of the soluble drug inside the tablet draws water through the semipermeable coating, resulting, in the formation of a saturated aqueous solution inside the device. The membrane is non-extensible and the increase in volume due to imbibition of water raises the hydrostatic pressure inside the tablet, eventually leading to flow of saturated solution of active agent out of the device through small orifice.

The dosage form, after coming in contact with the aqueous fluids, imbibes water at a rate determined by the fluid permeability of the membrane and osmotic pressure of core formulation. This osmotic imbibition of water results in formation of a saturated solution of drug within the core, which is dispensed at a controlled rate from the delivery orifice in the membrane. Though 60–80% of drug is released at a constant rate from EOP, a lag time of 30–60 min is observed in most of the cases as the system hydrates before zero-order delivery from the system begins. These systems are suitable for delivery of drugs having moderate water solubility.

Solubility of drug in water plays a critical role in functioning of osmotic pump. Typically the solubility of drug delivered by these pumps are at least 10 to 15% w/w, example of drugs with this property are sodium indomethacin, potassium chloride, metoprolol and acetazolamide (Santus and Baker, 1995).

Elementary osmotic pump for Indomethacin is reported in detail in a literature (Theeuwes et al., 1982) that explains the determination of theoretical release rate of Indomethacin elementary osmotic pumps. Using that concept, delivery of any agent in solution form from the elementary osmotic pump can be achieved at a rate proportional to the solubility of the agent inside the system (Sd) and the osmotic pressure of the formulation inside the system (π_t). Given a tablet size with surface area (A), and given the membrane permeability and thickness, the desired rate can be obtained by incorporating into the core formulation substances that affect either Sd or π_t. Such a formulation can be called as the composite core.

Delivery of potent agents may require the incorporation of formulating agents to permit fabrication of a system of acceptable size (these agents are also added during the

formulation of conventional tablets). If these agents are water soluble, system performance can be predicted from the knowledge of certain parameters and the theoretical considerations. The zero order release rate of drug, $(dm_d/dt)_z$, from such a system, assuming a negligible osmotic pressure of the environmental fluid, is then given by,

$$Z = \left(\frac{dm_d}{dt}\right)_z = K \frac{A}{h} \pi_t S_d \qquad (4)$$

Where K is the osmotic permeability coefficient of the membrane, A is the membrane area and h is the membrane thickness. The zero order rate will persist from time t=0 to $t=t_z$, at which time the solids, drug and osmotic agent have gone into solution. The non-zero order rate will decline parabolically as a function of time.

The above equation provides a convenient way of calculating the membrane permeability (k) for a set of systems with the same release rate. Alternatively for systems with different membrane thickness and release rates, the slope of the line of the release rate versus the inverse of the membrane thickness provides a means of calculating the membrane permeability. Consequently, the release rate can be expressed as a function of membrane weight (w), since this weight is related to membrane thickness.

$$w = \rho_m Ah. \qquad (5)$$

Where ρ_m is the membrane density, and by substituting above equation to the first equation,

$$Zd = K \frac{A^2}{w} \rho_m \pi_t S_d \qquad (6)$$

The membrane permeability, therefore, can be obtained from the slope of the line Z_d versus 1/w.

The final equation indicates the parameters to which the average zero order release rate will be sensitive. These parameters are, membrane permeability (k), tablet core surface are (A), membrane weight (W), density (ρ_m), total osmotic pressure (π_t) and drug solubility (S_d). When a composite composition is chosen, π_t and S_d become fixed for the zero-order release period. The fixed composition also determines the total surface area (A) of the tablet core. When the membrane is chosen and applied reproducibility, values

for K and π_m are fixed. Therefore, when testing is conducted at a constant temperature, the average zero order release rate should be a function of the weight of the membrane applied.

Alza is the leading pharmaceutical concern which developed the elementary osmotic pump under the trade name OROS®, for oral controlled release. The first elementary osmotic pump that hit international market was Osmosin® (controlled release Indomethacin).

PRODUCTS INCORPORATING ALZA'S OROS® TECHNOLOGY INCLUDE

- Alpress™ LP (prazosin) once-daily extended-release tablet sold in France for the treatment of hypertension.
- Cardura® XL (doxazosin mesylate) sold in Germany for the treatment of hypertension.
- Concerta® (methylphenidate HCl) CII once-daily extended-release tablet for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients age six and older.
- Covera-HS® (verapamil) a Controlled Onset Extended Release (COER-24™) system for the management of hypertension and angina pectoris.
- Ditropan XL® (oxybutynin chloride) extended-release tablet for the once-a-day treatment of overactive bladder characterized by symptoms of urge urinary incontinence, urgency and frequency.
- DynaCirc CR® (isradipine) once-daily, extended-release tablet for the treatment of hypertension.
- Efidac 24® (chlorpheniramine) over-the-counter, extended-release tablet providing 24-hour relief from allergy symptoms and nasal congestion.
- Glucotrol XL® (glipizide) extended-release tablet used as an adjunct to diet for the control of hyperglycemia in patients with non-insulin-dependent diabetes.
- Sudafed® 24 Hour (pseudoephedrine) over-the-counter nasal decongestant for 24-hour relief of colds, sinusitis, hay fever and other respiratory allergies.

- Procardia XL® (nifedipine) extended-release tablet for the treatment of angina and hypertension.
- Volmax® (albuterol) extended-release tablet for relief of bronchospasm in patients with reversible obstructive airway disease.

In the OROS tablets, semipermeable membrane coating of the device must be 200-300 microns thick to withstand the pressure generated within the device. These thick coverings however, lower the water permeation rate, particularly for moderately water-soluble drugs. In general it could be predicted that these thick coating devices are suitable for highly water-soluble drugs. The delivery rate attained with moderately soluble drugs is generally low, even with the most water permeable membrane also. The above problem can be resolved by utilizing a coating material having very high water permeability, such as addition of plasticizers and a water-soluble additive to the cellulose acetate membranes which increased the permeability of latter up to tenfold. (Theeuwes and Ayer, 1978).

The second approach of Theeuwes involves the multi layer composite coating around the tablet (Fig. 1.3). The first layer is made up of thick microporous film that provides the strength required to withstand the internal pressure, while second layer is composed of thin semi permeable membrane that produces the osmotic flux. The support layer is formed by including the coating of the tablets with a layer of cellulose acetate containing 40 to 60% of pore forming agent such as sorbitol.

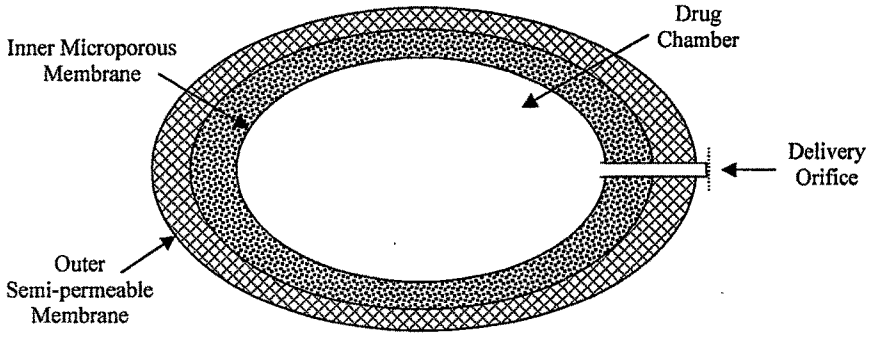

Fig. 1.3 Composite membrane coating used to deliver moderately soluble drugs

Another modification includes the addition of a carbonate or bicarbonate salt to the drug chamber, which eventually leads to effervescence when exposed to water due to formation of carbon dioxide at stomach pH.

The simple elementary osmotic pump suffers from the disadvantage that it can only deliver relatively soluble drugs, which are capable of developing an osmotic pressure greater than physiological fluids. Incorporation of water-soluble compound into the tablet formulation such as, sodium chloride, sucrose, fructose or other common tableting aids can be used, which serves as osmotic attractants and overcomes this limitation.

Several coated tablet have been reported (Zentner et al,1985) in which the drug escapes, following leaching of water soluble components, such as lactose or polyethylene glycol from the coating material. Once the tablet has been swallowed, water-soluble component dissolves in external fluid, resulting in initiation of pumping system.

Shokri et al., (2007) designed a new type of elementary osmotic pump (EOP) tablet for efficient delivery of poorly water-soluble/practically insoluble drugs. The drug release profile from osmotic devices showed that the type of polymer in the core formulation could markedly affect the drug release. The results also demonstrated that aperture size is a critical parameter and should be optimized for each swellable EOP system. This study also revealed that optimization of semipermeable membrane thickness is very important for approaching zero order kinetics.

- ***PUSH–PULL OSMOTIC PUMP (PPOP)***

Push–pull osmotic pump (PPOP) can be used for delivery of drugs having extremes of water solubility. As shown in Fig. 1.4, it is a bilayer tablet coated with a semipermeable membrane. Drug along with osmogents is present in the upper compartment whereas lower compartment consists of polymeric osmotic agents (Swanson et al., 1987, Wong et al., 1986,). The drug compartment is connected to the outside environment via a delivery orifice. After coming in contact with the aqueous environment, polymeric osmotic layer swells and pushes the drug layer, thereby delivering the drug in the form of a fine dispersion via the orifice (Grundy et al., 1996).

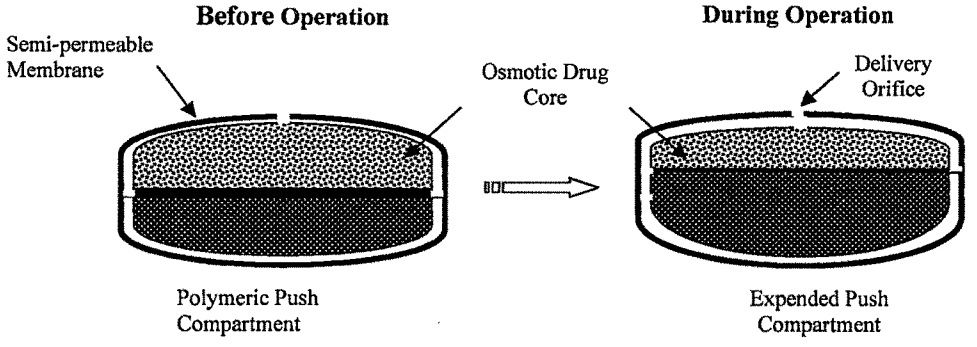

Fig. 1.4 Drug delivery process from two-chamber osmotic tablet

Pumps with two chambers separated by an elastic or movable barrier are particularly interesting and valuable because they allow delivery of drugs with limited solubility. This class of osmotic pump can further be classified into two groups, one with internal film that moves from a rest to an expanded state leading to change in volume of chamber. The second group has fixed volume chamber communicating through opening provided in between.

Swanson et al. (1987) formulated a dosage form based on the gastrointestinal therapeutic system (GITS) push pull osmotic pump configuration in three strengths with different drug delivery rates(mg/hour) per dose (mg), as 1.7/30, 3.4/60, and 5.1/90. The delivery rates of drug from these systems are controlled by drug loading, composition of osmotic components, membrane properties, and dimensions. The release rates were independent of pH in the range from gastric pH 1.2 to intestinal pH 7.5. *In vitro* release studies were carried out at different stirring rates (50, 100, 150 rpm). The release rates are independent of stirring rate and therefore unlikely to be influenced by motility in the gastrointestinal tract. The in-vivo release tests in dogs were found to be equal to the release rate in-vitro. Nifedipine GITS dosage forms were administered to human subjects, absorption rates, calculated from resulting plasma concentrations, indicate that the cumulative amount of drug absorbed in humans over 24 hours is proportional to the amounts of drug delivered in-vitro. Plasma concentrations are therefore predictable and remain relatively constant through out the 24 hour dosing interval. Weight of drug layer, weight of push layer, membrane thickness, and membrane permeability along with the delivery rates was reported. Comparison of in-vitro and in-vivo cumulative amount released was shown.

Among the successful approaches incorporation of finely dispersed drug in hydrogel present a most valuable alternative. Many of the useful hydrogel polymers are ionic materials such as sodium carboxy methylcellulose, which contains ionizable groups, which provide most of the osmotic pressure required to draw water through the semipermeable membrane. These polymers possess dual property of being compressed in dry conditions and become fluid gels, which are easily extrudable through the small delivery hole in hydrated conditions. A number of modifications are available for this type of system such as delayed push–pull system (as used in Covera HS, extended release formulation for verapamil), multi-layer push–pull system (for pulsatile or delayed drug delivery), and push–stick system (for delivery of insoluble drugs requiring high loading, with an optional delayed, patterned, or pulsatile release profile)

- ***OROS-CT***

OROS-CT is used as a once or twice-a-day formulation for targeted delivery of drugs to the colon (Verma et al., 2002). The OROS-CT can be a single osmotic unit or it can comprise of as many as five to six push–pull osmotic units filled in a hard gelatin capsule (Fig. 1.5).

After coming in contact with the gastrointestinal fluids, gelatin capsule dissolves and the enteric coating prevent entry of fluids from stomach to the system. As the system enters into the small intestine, the enteric coating dissolves and water is imbibed into the core

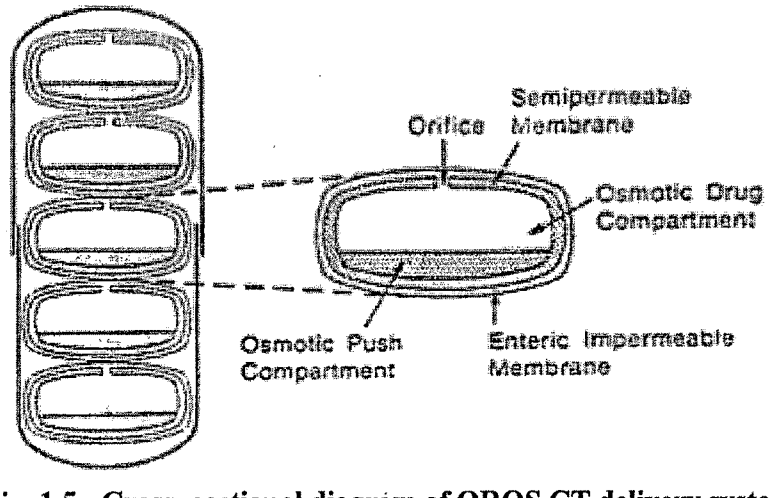

Fig. 1.5 : Cross- sectional diagram of OROS CT delivery system

thereby causing the push compartment to swell. At the same time, flowable gel is formed in the drug compartment, which is pushed out of the orifice at a rate that is precisely controlled by the rate of water transport across the SPM.

For OROS® tablets coated with dense membrane coatings, the semipermeable membrane must be 200- 300 microns thick to withstand the pressure generated within the device. Because these membranes are thick, the water permeation rate is low, particularly if the drug is moderately soluble and has a low osmotic pressure. In general, tablets coated with dense membranes are suitable for delivering highly water-soluble drugs. The delivery rate achievable with moderately soluble drugs is usually low, even with the most water-permeable membranes.

➢ ***LIQUID OROS (L-OROS)***

L-OROS controlled release systems are designed to deliver drugs as liquid formulations and combine the benefits of extended-release with high bioavailability (Dong et al., 2000). Fig. 1.6 shows the cross-sectional diagram for L-OROS SOFTCAP delivery system before and during operation. These systems are suitable for controlled delivery of liquid drug formulations including lipophilic self-emulsifying formulations (SEF). The liquid drug formulation is present in a soft gelatin capsule, which is surrounded with the barrier layer, the osmotic layer, and the release rate controlling membrane. A delivery orifice is formed through these three layers. When the system is in contact with the aqueous environment, water permeates across the rate controlling membrane and activates the osmotic layer. The expansion of the osmotic layer results in the development of hydrostatic pressure inside the system, thereby forcing the liquid formulation to break through the hydrated gelatin capsule shell at the delivery orifice. The liquid drug formulation is pumped through the delivery orifice. L-OROS HARDCAP is similar to L-OROS SOFTCAP and consists of a liquid drug layer, a barrier layer, and an osmotic engine, all encased in a hard gelatin capsule and coated with a SPM (Dong et al., 2001). A delivery orifice, drilled in the membrane at the end of the drug layer, provides an outlet for the drug suspension. After coming in contact with the aqueous environment, water is imbibed across the SPM, expanding the osmotic engine. The osmotic engine pushes against the barrier, releasing drug through the delivery orifice.

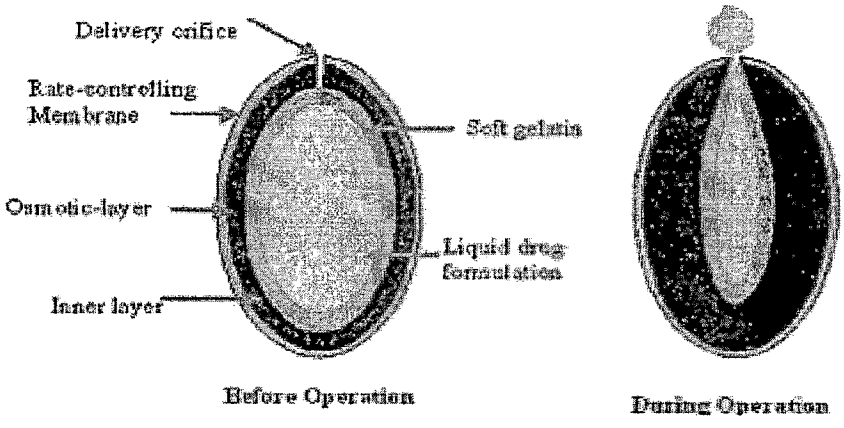

Fig. 1.6 Cross- sectional diagram of L–OROS delivery system before and during operation

In majority of cases, osmotic systems have a pre-formed passageway in the membrane from where the drug release takes place.

➢ ***CONTROLLED POROSITY OSMOTIC PUMPS (CPOP)***

CPOP contain water-soluble additives in the coating membrane, which after coming in contact with water, dissolve resulting in an in situ formation of a microporous membrane (Fig. 1.7). The resulting membrane is substantially permeable to both water and dissolved solutes and the mechanism of drug release from these systems was found to be primarily osmotic, with simple diffusion playing a minor role (Zentner et al., 1985a).

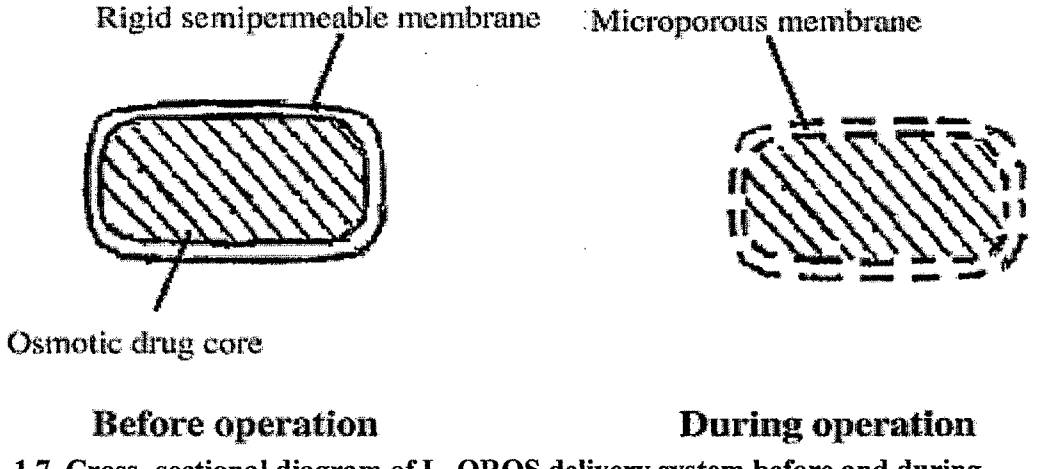

Fig. 1.7 Cross- sectional diagram of L–OROS delivery system before and during operation

Zentner et al., (1985a) developed a controlled porosity osmotic pump of cyclobenzaprine hydrochloride. The coating solution applied to the core was Cellulose Acetate-398-30: sorbitol : polyethylene glycol 400 (10 : 7.5 : 1 by parts) dissolved in DCM:methanol:water.

Verma et al., (2003) developed extended release formulations of isosorbide mononitrate based on osmotic technology. Formulation variables like type (PVP, PEG 4000 & HPMC) and level of pore former, per cent weight gain were found to affect the drug release from the developed formulations. Drug release was inversely proportional to the membrane weight but directly related to the initial level of pore former in the membrane. Burst strength of the exhausted shells was inversely proportional to the level of pore former, but directly affected by the membrane weight. The release from the developed formulations was independent of pH and agitation intensity, but depended on the osmotic pressure of the release media. Results of SEM studies showed the formation of pores in the membrane from where the drug release occurred.

Gondaliya and Pundarikakshudu (2003) developed a controlled porosity osmotic pump of diltiazem hydrochloride. *In vitro* dissolution studies of tablets were conducted in osmotically active media. The external osmotic pressure was maintained at higher levels than the osmotic pressure generated inside the tablet. The drug release rate was tested in a 2.4% (by weight) magnesium sulfate solution (6 atm pressure) and water (0 atm pressure). An *in vitro* release rate was found to be 2.2 mg/h in a magnesium sulfate solution, although in water it was found 10.6 mg/h. In the magnesium sulfate solution, the drug release rate was mainly attributed only to diffusion through the membrane, although in water, the drug release rate was mainly attributed to diffusion and osmosis. High *in vitro* drug release was mainly attributed to osmotic pressure generated inside the osmotic tablets. In an osmotically active medium, the osmosis phenomenon is stopped. These results were further confirmed by performing in *vitro* drug release study by changing the medium instead of the method. An *in vitro* drug release study was conducted for 0- 4 h in water (0 atm pressure) followed by 4- 8 h in a 2.4% (by weight) magnesium sulfate solution (~6 atm pressure) followed by 8- 12 h in water. The results showed a significant difference in the release rate in different media. From these results, one may conclude that the drug release from the tablets was mainly caused by diffusion in an osmotically

active medium. *In vitro* release was carried out in a USP type II dissolution test apparatus at 100 rpm. Operating condition was 900 ml of distilled water at 37°C. Coating membrane was composed of cellulose acetate as film forming polymer, glycerol as pore forming agent and dibutylpthalate as a plasticizer. An equal portion of isopropyl alcohol and acetone was used as a coating solvent.

Verma and Garg (2004) developed controlled porosity osmotic pump of glipizide. To assure a reliable performance of this formulation independent of pH, release studies were conducted according to pH change method. The release media was simulated gastric fluid (SGF, pH 1.2) for first 2 h, acetate buffer (pH 4.5) for next 2 h, followed by SIF (pH 6.8) for the remaining period of 24 h. In order to study the effect of agitational intensity of the release media, release studies of the formulation were carried out in dissolution apparatus at various rotational speeds using USP-I dissolution apparatus (rotating basket) at 50, 100, and 150 rpm. In another experiment, stirred and stagnant conditions were induced in a single run using USP-I apparatus. The rotational speed was kept at 100 rpm (stirred conditions), which was stopped intermittently to induce the stagnant conditions. The protocol used was stirred conditions for first 3 h (0–3 h), stagnant conditions for next 2 h (3–5 h), stirred condition for next 3 h (5–8 h), and stagnant condition for next 2 h (8–10 h). In order to confirm the mechanism of drug release, release studies of the formulation were conducted in media of different osmotic pressure. To increase the osmotic pressure of the release media, sodium chloride (osmotically effective solute) was added in SIF and the pH was adjusted to 6.8 $\pm$ 0.05. Release studies were carried out in 1000 ml of media using USP-I dissolution apparatus (100 rpm). Release from the formulation was inversely proportional to the osmotic pressure of the release media, conforming osmotic pumping to be the major mechanism of drug release.

- ***ASYMMETRIC MEMBRANES***

Use of asymmetric membranes in osmotic drug delivery that consist of very thin, dense skin structure supported by a thicker, porous structural layer is also described in the literature (Herbig et al., 1995). These membranes have high flux characteristics and thus, higher release rates for poorly water-soluble drugs can be obtained. Moreover, the permeability of the membranes to water can be easily adjusted by controlling the

membrane structure and porosity. The asymmetric membranes can be applied to tablets, capsules, or multi-particulate formulations.

Herbig et al.,(1995) developed a new type of membrane coating for osmotic drug delivery which offers significant advantage over the membrane coatings used in conventional osmotic tablets. These new coatings have an asymmetric structure, similar to asymmetric membranes made for reverse osmosis or ultra filtration, in that the coating consists of a porous substrate with a thin outer skin. These asymmetric membrane coatings can be used to make osmotic drug delivery formulations with several unique characteristics. High water fluxes can be achieved, facilitating osmotic delivery of drugs with low solubility and making higher release rates possible. The permeability of the coating to water can be adjusted by controlling the membrane structure. Thereby allowing control of the release kinetics without altering the coating material or significantly varying the coating thickness. In addition the porosity of the film can be controlled, minimizing the time lag before drug delivery begins and allowing the drug to be released from a large number of delivery ports. The type of coatings have also been applied to capsule and multi particulate formulations.

Lin and Ho (2003) formulated asymmetric membrane coated capsules with in-situ formation of delivery orifice. The capsule wall membrane was produced by phase inversion process in which an asymmetric membrane was formed on stainless steel mold pins by dipping the mold pins into a coating solution containing a polymeric material followed by dipping into a quenching solution. Permeability across the asymmetric membrane of the capsule was determined for drugs with water solubility in a moderate to high range. Poorly soluble drug could not generate enough osmotic pressure to activate drug release. Solubilization either by the addition of solubility enhancer, SLS, or by a solid dispersion with HPMC could increase the solubility of nifedipine to a sufficient extent to activate drug release. Synergistic action of both HPMC and SLS increased the solubility of nifedipine resulting in release from the system.

- ***SANDWICHED OSMOTIC TABLET SYSTEM (SOTS)***

In SOTS, a tablet core consisting of a middle push layer and two attached drug layers is coated with a semipermeable membrane (Liu et al., 2000). Both the drug layers are connected to the outside environment via two delivery orifices (one on each side). After coming in contact with the aqueous environment, the middle push layer containing swelling agents swells and the drug is released from the delivery orifices. The advantage with this type of system is that the drug is released from the two orifices situated on two opposite sides of the tablet and thus can be advantageous in case of drugs which are prone to cause local irritation of gastric mucosa.

Liu et al., (2000a) prepared sandwiched osmotic tablet system (SOTS) which is composed of a sandwiched osmotic tablet core surrounded by cellulose acetate membrane with two orifices on both side surfaces, has been successfully prepared with the purpose of delivering nifedipine. SOTS contain a middle push layer and two attached drug layers. Influences of tablet formulation variables, orifice size and membrane variables on nifedipine release of SOTS have been studied. The appropriate orifice size was observed in the range of 0.5-1.41 mm. It was also found that the drug release rate of SOTS could be increased by incorporating hydrophilic plasticizer in the membrane.

CURRENTLY REPORTED NOVEL OSMOTIC PUMPS

➢ *MOTS (MONOLITHIC OSMOTIC PUMP TABLET)*

Liu and Wang (2007) developed a method for the preparation of monolithic osmotic pump tablet by modulating atenolol solubility with acid. The formulation of atenolol monolithic osmotic pump tablet was optimized by orthogonal design and evaluated by similarity factor (f2). The optimal monolithic osmotic pump tablet was found to be able to deliver atenolol at the rate of approximate zero-order up to 24 h, independent of release media and agitation rate. The approach of solubility-modulated by acid-alkali reaction might be used for the preparation of osmotic pump tablet of other poorly water-soluble drugs with alkaline or acid groups.

Liu et al., (2000b) developed the monolithic osmotic tablet system, which is composed of a monolithic tablet coated with cellulose acetate membrane drilled with two orifices on both sides surface, has been described. The influences of tablet formulation variables

including molecular weight and amount of polyethylene oxide amount of potassium chloride and amount of rice starch as well as nifedipine loading have been investigated. Orifice size and membrane variables including amount of plasticizers as well as thickness on drug release have also been studied. The in-vitro release profiles of optimal system have been evaluated in various release media and different agitation rates, and compared with conventional capsule and push pull osmotic tablet. It was found that orifice size range of 0.25-1.41 mm was optimum. Both hydrophilic and hydrophobic plasticizers were investigated to note the influence on drug release. Release studies were performed on different pH media, different agitation intensities.

- ***MTCT-OP (MICROBIALLY TRIGGERED COLON-TARGETED OSMOTIC PUMP)***

Liu et. al., (2007) studied a microbially triggered colon-targeted osmotic pump (MTCT-OP). The gelable property at acid condition and colon-specific biodegradation of chitosan were used to: (1) produce the osmotic pressure, (2) form the drug suspension and (3) form the in situ delivery pores for colon-specific drug release, respectively. The different levels of enteric-coating membrane could prevent cellulose acetate membrane (containing chitosan as pore former) from forming pore or rupture before contact with simulated colonic fluid, but had no effect on the drug release. These results showed that MTCT-OP based on osmotic technology and microbially triggered mechanism had a high potential for colon-specific drug delivery.

- ***SCT (SWELLABLE CORE TECHNOLOGY)***

Thombre et al., (2003) developed swellable core technology (SCT) formulations that used osmotic pressure and polymer swelling to deliver drugs to the GI tract in a reliable and reproducible manner were studied. SCT formulations consisted of a core tablet containing the drug and a water swellable component and one or more delivery ports. The in-vitro and in-vivo performance of two model drugs Tenidap and Sildenafil, formulated in four different SCT core configurations; homogeneous core, tablet in tablet , bilayer and trilayer core, were evaluated. Release studies indicated that the drug release rate was relatively independent of the core configuration but the extent of release was somewhat lower for the homogeneous core formulation particularly under non sink

conditions. The in-vivo studies conducted in beagle dogs revealed that the in-vivo release of drug from SCT formulation was comparable to the in-vitro drug release.

OSMOTIC PUMPS AND SOLUBILITY OF DRUGS

Osmotic pumps are well known for delivering drugs at a zero order rate. The associated limitation with respect to formulation is that both highly water soluble and highly water insoluble drugs are not suitable candidates. The kinetics of osmotic drug release is directly related to the solubility of the drug within the core. Assuming a tablet core of pure drug, the fraction of core released with zero-order kinetics is given by the following equation (Eq.7) (McClelland et al., 1991, Zentner et al., 1991),

$$F(z) = 1 - \frac{S}{\rho} \qquad (7)$$

where $F(z)$ is the fraction released by zero-order kinetics, S is the drug's solubility (g/ cm^3), and ρ is the density (g / cm^3) of the core tablet. Drugs with a solubility of ≤ 0.05 g/ cm^3 would be released with $\geq 95\%$ zero-order kinetics. Hence a solubilizer for the drug can be included in the core formulation in case of water insoluble drugs. It is also possible that the drug is very highly soluble and the water flux is too great to provide sustained release. In this case, the core can include a component that suppresses the solubility of the active agent.

Some of the approaches that have been used to deliver drugs having extremes of solubility are:

➢ ***CO-COMPRESSION OF DRUG WITH EXCIPIENTS:***

Incorporation of excipients that modulate the solubility of drug within the core can be one approach to control the release of drugs from the osmotic systems. McClelland et al. (1991) and Zentner et al. (1991) reported CPOP of a highly water-soluble drug, diltiazem hydrochloride (solubility more than 590 mg/ml at 37 8C). Because of very high water-solubility, the majority of the drug fraction was released predominantly at a first-order rather than the desired zero-order rate. The solubility of diltiazem hydrochloride was reduced to 155 mg/ml by incorporation of sodium chloride (at 1 M concentration) into the

core tablet formulation. The modification resulted in more than 75% of the drug to be released by zero-order kinetics over a 14–16-h period.

Controlled porosity solubility modulated osmotic pumps for delivery of drugs having low water solubility are described in US Patents (McClelland and Zentner, 1990, Zentner and McClelland, 1991). The composition described consists of controlled release solubility modulating agents, which are either surfactants (e.g. sodium dodecyl sulfate) or complexing agents (e.g. sodium salicylate). In order to prolong the availability of these excipients within the device, they were either surrounded by a rate controlling membrane or dispersed in a matrix. In the examples, tablet cores of two different drugs, namely, simvastatin and lovastatin, along with the solubility modulating agents were prepared and coated with a microporous membrane. The release of drug from the systems was controlled for an extended period of 4–24 h.

Prabakaran et al., (2003) formulated elementary osmotic pump for diltiazem hydrochloride. The drug candidate selected shows higher aqueous solubility, and hence is an unfit candidate for the formulation of elementary osmotic pumps. To control the solubility of the drug in the core various hydrophilic polymers (HPMC & NaCMC) were incorporated and the otherwise fast dissolving core was altered to release the drug for the prolonged period. Ingredients of the system were optimized for parameters like drug polymer ratio and amount of osmogent, for the desired release pattern. The coated tablets were drilled mechanically in the centre of each pump. The aperture diameter and coating thickness were measured microscopically using empty shells obtained after complete dissolution of the contents. Different dissolution models were applied to drug release data in order to establish release mechanism and kinetics. Criteria for selecting the most appropriate model were based on best goodness of fit and smallest sum of squared residuals.

- ***USE OF ENCAPSULATED EXCIPIENTS***

Thombre and coworkers (Thombre 1997 and Thombre et al. 1999) described a capsule device coated with asymmetric membranes to deliver drugs having poor water-solubility. In the examples, solubility of a poorly water-soluble drug, glipizide, was improved by incorporation of encapsulated excipients (pH-controlling excipients) within the capsule device. The solubility modifier (meglumine), in the form of mini-tablets, was coated with

a rate controlling membrane to prolong its availability within the core. Thus, the solubility of glipizide was improved leading to its prolonged release from the device.

➢ ***USE OF SWELLABLE POLYMERS***

Swellable polymers can be utilized for osmotic delivery of drugs having poor aqueous solubility. Examples using this approach are reported in US Patent (Khanna, 1991) for carbamazepine, theophylline, acetylsalicylic acid, and nifedipine. The formulation mainly consists of a compartment, containing the drug, swelling agents, and osmogents, coated with a rate controlling membrane. Vinylpyrrolidone / vinyl acetate copolymer (Kollidon VA 64, BASF) and polyethylene oxide (MW: 53 10 , Polyox -coagulant, Union Carbide) were used as swelling agents. Uniform rate of swelling of these polymers ensures that the drug is released at a relatively constant rate. Also, the pressure produced during swelling does not lead to rupture of the system.

Sastry et al., (1997) prepared and evaluated an optimized, osmotically controlled formulation of atenolol. Preparation involved the fabrication of biconvex, bilayered tablets containing drug, an osmotic agent and other additives. Studies on the screening of several variables have revealed that orifice size, coating level and the amount of carbopol have pronounced effects on the in vitro release kinetics of atenolol. For formulation optimization a three factor, three level Box-Behnken design was employed with independent variables of orifice size, coating level and the amount of carbopol. The response variables was cumulative per cent of atenolol released with constrains of time for certain percentage release. Preparation of optimized formulations showed a good correlation between predicted and observed values

➢ ***USE OF EFFERVESCENT MIXTURES***

Use of effervescent mixture, can be another approach to deliver poorly water-soluble drugs from osmotic dosage forms. After administration, the effervescent mixture containing the drug is delivered under pressure through the delivery orifice in the membrane. This method of enhancing release of poorly water-soluble drug is reported in US Patent (Theeuwes, 1977). In one of the examples, citric acid and sodium bicarbonate were used as the effervescent couple for the delivery of acetyl salicylic acid. The

formulation imbibes aqueous fluids across the membrane causing the couple to generate an effervescent solution that dispenses the drug in a suspension form.

➢ ***USE OF CYCLODEXTRIN DERIVATIVES***

Incorporation of the cyclodextrin–drug complex has also been used as an approach for delivery of poorly water-soluble drugs from the osmotic systems. A CPOP has been described for testosterone (having a solubility of 0.039 mg/ml at 37 °C), solubility of which was improved to 76.5 mg/ml through complexation with sulfobutyl ether-β-cyclo dextrin sodium salt (Okimoto et al., 1999a). In a comparative study with hydroxypropyl-β-cyclodextrin (HP-β-CD) and a sugar mixture, it was found that testosterone release from the device in the presence of sulfobutyl ether-β-cyclo dextrin sodium salt was mainly due to osmotic pumping while for HP-β-CD, the major contribution was due to diffusion. In case of the sugar mixture, the drug was poorly released due to the absence of solubilizer. Similar results were obtained with prednisolone (Okimoto et al., 1998) and chlorpromazine (Okimoto et al., 1999b). It was reported that sulfobutyl ether-β-cyclo dextrin sodium salt could serve both as a solubilizer and osmotic agent.

Okimoto et al., (1999c) defined membrane controlling factors responsible for drug relase from a controlled porosity osmotic pump tablet that utilizes a sulfobutyl ether-β-cyclodextrin, as both a solubilizing and osmotic agent. Chlorpromazine was used as a model drug. The core tablets were coated with cellulose acetate solutions varying the amount and size of micronized lactose, the amount of triethyl citrate and composition ratio of dichloromethane to ethanol. The membrane surface area of the coated tablet were measured with multi point analysis by the gas absorption method. The relase rate of drug from osmotic pumps increased with increasing amounts of micronized lactose and decreasing amount of TEC and lactose particle size in the membrane. Also, release rates from the formulations using mixtures of varying ratios of dichloromethane to ethanol were almost identical.

➢ ***RESIN MODULATION APPROACH***

Release of a highly water-soluble drug, diltiazem hydrochloride from a CPOP was modulated effectively using positively charged anion-exchange resin, poly (4-vinyl

pyridine) (Zentner et al., 1991). Pentaerythritol was used as osmotic agent and citric and adipic acids were added to maintain a low core pH to assure that both the drug and resin carry a positive charge. The solubility of diltiazem hydrochloride was reduced for an extended period and pH-independent zero-order release was obtained.

➢ ***USE OF ALTERNATIVE SALT FORM***

For an ionic drug, an alternative salt form can also be used as reported for metoprolol and oxprenolol (Theeuwes et al., 1985). Hydrochloride salt used in commercial formulations of oxprenolol was found to have high water solubility (70% w/v) making it difficult to achieve extended zero-order delivery from osmotic systems. The authors replaced it by the less soluble succinate salt. In case of metoprolol, they used fumarate salt form as drug and osmotic driving agent, instead of tartrate salt. These salt forms were found to have optimum solubility and provided extended release up to 24 h.

➢ ***USE OF CRYSTAL HABIT MODIFIERS***

If the drug exists in more than one crystal form, each having different aqueous solubility, it is beneficial to include a crystal modifying agents. One such example is reported in US Patent (Koparkar and Shah, 1994), wherein a slightly soluble drug, carbamazepine, along with crystal modifying agents (combination of hydroxymethyl cellulose and hydroxyethyl cellulose) and other excipients was formulated in the form of osmotic pumps that were able to provide approximately zero-order release for the desired period of time.

➢ ***USE OF LYOTROPIC CRYSTALS***

Use of lyotropic liquid crystals, to assist osmotic delivery of poorly water soluble drugs, is also reported in the literature (Curatolo, 1989 and 1992). The lyotropic liquid crystals are non-polymeric compounds, generally in the molecular weight range of 200–1500. Also known as amphipathic compounds, these form mesophases and swell in presence of water. Compounds that can be used as lyotropic liquid crystals include natural phosphatides such as phosphatidyl- choline (lecithin), phosphatidylethanolamine, phosphatidylserine, phosphatidylglycerol, and the like. Few examples using this approach are mentioned in US Patent no. 5,108,756 and 5,030,452. In these examples, Alcolec lecithin (American Lecithin Co., Atlanta, GA) and mixture of soybean phospholipids was

utilized for osmotic delivery of two insoluble drugs, namely, glipizide and prazosin. The inventors claimed that the extended drug release up to 24 h was achieved.

➢ ***USE OF WICKING AGENTS***

Inclusion of wicking agents in the osmotic formulations has also been reported as an approach for poorly water-soluble drugs (Rudnic et al., 2000). A wicking agent is dispersed throughout the composition that enhances the contact surface area of drug with the incoming aqueous fluids. Thus, the drug is released predominantly in a soluble form through the delivery orifice in the membrane. The authors delivered nifedipine using this approach and some of the reported wicking agents are colloidal silicon dioxide, PVP, sodium lauryl sulfate, etc.

REPORTED IN-VITRO EVALUATION OF OSMOTIC SYSTEM IN LITERATURE

Rani et al., (2003) developed an elementary osmotic pump for diclofenac sodium. To study the effect of pH, dissolution was carried out in USP II apparatus in different release media (pH 7.4, pH 6.8, and distilled water) maintained at 37 + 0.2 °C and 100 rpm which resulted in a non-significant difference in release. To study the effect of agitation intensity, in vitro studies were performed at 50 rpm, 100 rpm, and under static conditions. Under static conditions, samples were taken at different times after uniform mixing of the media. Studies under stirred and static conditions exhibited no significant difference in the rate and extent of release. In vitro studies were done using a USP 24 dissolution apparatus II at 100 rpm.

Zentner et al.,(1985b) developed a controlled porosity osmotic pump of potassium chloride. To study the effect of pH of release media on drug release, release study was conducted in deionized water and various other aqueous receptor media at 37 °C. Experiments at pH 5, 7.4, and 8 were conducted in 0.07 M Sorensen's phosphate buffer. Studies at pH 1 were in 0.1 N hydrochloric acid. Wherever required, pH adjusted media were made iso-osmotic to normal saline by adding sodium chloride. The following patterns of stirring were employed in the release studies, 100 rpm continuously and 100 rpm interrupted with a 2 hour period of no stirring at the midpoint of the steady state

release profiles. The effects of receptor media osmotic pressure on potassium chloride release were studied in 1.64, 3.42, 7.06, and 11.63 molal aqueous solutions of urea at 25 °C. Coating solution composed of cellulose acetate, sorbitol and PEG 400 as film forming polymer, pore forming agent, and plasticizer, respectively. Solvent was a quaternary mixture of dichloromethane, methanol, water, and polyethylene glycol 400 mixed 150: 100: 10: 1 by weight respectively, as dictated by the solubility of the solid components that were incorporated.

Makhija and Vavia (2003) developed a controlled porosity osmotic pump of pseudoephedrine. As a proof of an osmotically controlled release system, (delivers its contents independent of external variables) the *in vitro* release studies were conducted in buffers of different pH, i.e., pH 1.2 buffer, pH 4.5 phosphate buffer and pH 7.2 phosphate buffer as well as in distilled water. The system exhibits a media independent release. Thus, the fluid in different parts of the GI tract will scarcely affect drug release from the osmotic system. The *in vitro* release from the coated tablets was studied using USP dissolution apparatus type I at 100 rpm. The dissolution medium used was 500 ml of phosphate buffer of pH 7.2. The tablets were coated with cellulose acetate as semipermeable film forming polymer containing different channeling agent viz. diethylphthalate, dibutylpthalate, dibutylsebacate, and polyethylene glycol 400. Talc and titanium dioxide were used as antiadherant and opacifier respectively. Acetone: isopropyl alcohol (80:20) was used as a coating solvent.

Verma and Garg (2004) developed controlled porosity osmotic pump of glipizide. The *in vitro* release was carried out in a USP type 1 dissolution apparatus at 100 rpm. Dissolution medium was simulated intestinal fluid (SIF, pH 6.8, 1000 ml) maintained at 37 $\pm$ 0.5°C. Coating membranes was consisting of cellulose acetate as film forming polymer. PVP was used as a water-soluble component. PEG 400 and triacetin were used as a water-soluble and water insoluble plasticizer respectively. Dichloromethane : methanol (3:1) were used as a coating solvent.

Garg et. al., (2007) studied the effect of formulation parameters on the release characteristics of propranolol from asymmetric membrane coated tablets. A zero order release of propranolol was obtained from the coated tablets of propranolol. The release was independent of the pH and the rate of agitation of the dissolution medium ($p > 0.05$).

Asymmetric membranes could be successfully utilized in the controlled delivery of highly water soluble drugs like propranolol and by modifying preparation parameters like polymer concentration, pore former concentration and temperature of the precipitation bath, desired release rates can be obtained.

RESEARCH ENVISAGED

The aim of present research was to design and optimize the following three novel osmotic drug delivery systems for water soluble and low water soluble drugs and compare. (See Table 1.2).

1. Swellable Porous Osmotic System (SPOP)
2. Monolithic Osmotic Tablet System (MOTS)
3. Controlled Porosity Osmotic System (CPOP)

Table 1.2 Details of osmotic technologies and the drug candidates

Sr. no.	Technology	Water soluble drug	Low water soluble drug
1.	Swellable Porous Osmotic System / (SPOP)	Venlafaxine HCl	Glipizide
2.	Monolithic Osmotic Tablet System / (MOTS)	Metoprolol tartrate	Nifedipine
3.	Controlled Porosity Osmotic System / (CPOP)	Oxybutynin chloride	Atenolol

SPOP

The aim of the current study was to design a novel swellable porous osmotic pump (SPOP) based drug delivery system using various viscosity grade polymers of hydrophilic polymers, hydroxypropyl methylcellulose (HPMC) as swellable pore

formers, for controlled release of highly water soluble drug, venlafaxine HCl (VH) and water insoluble drug glipizide (GZ). The current study was also focussed on the effect of various viscosity grade pore formers, HPMC K100LV, HPMC K4M and HPMC K15M. In case of VH, effects of various ratios of drug to osmogent on the drug release were studied. In order to enhance the solubility of GZ, meglumine was used as solubilizing agent in the core formulation and the quantity was optimised.

The SPOP controlled-release system is based on hydrophilic polymer coating. When the formulation is administered orally and reaches the stomach, gastric fluid enters the core through semipermeable membrane and dissolves the water soluble osmotically active agent (osmogent) and creates osmotic pressure in the core. Meanwhile, high viscosity grade swellable agent (s) present in the coating film swells and creates sponge like appearance in the membrane. The drug release occurs through the sponge like structure by osmotic mechanism. As formulation moves through the gastrointestinal tract, high viscosity grade swellable agent (s) present in the coating film swell and create more sponge like structure in the membrane and the drug release occurs through theses sponge like structure by osmotic mechanism. The formation of number of sponge like structure is irrespective of pH and time, and drug release occurs continuously by osmotic mechanism. The mechanisms by which drug release is controlled in SPOP system are dependent on many variables. One of the principles of drug release would be osmotic pressure. However, it is obvious that the water-soluble polymer, coated throughout the tablet, hydrates on the tablet surface to form a gel layer and the drug molecules are diffused out and hence the diffusion mechanism cannot be ruled out for the present study (see Fig 1.8).

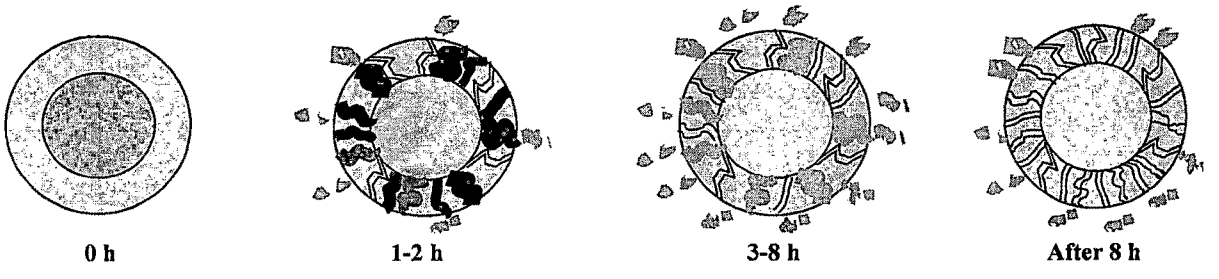

Fig. 1.8 Release mechanism from a proposed Swellable Porous Osmotic System (SPOP)

It is possible that one can modulate the release profile of the water soluble, sparingly soluble and poorly soluble active agents by changing the proportion of the semipermeable polymer, pH insensitive high viscosity grade swellable agent (s).

MOTS

The aim of the current study was to design a novel monolithic osmotic tablet system (MOTS) based drug delivery system for controlled release of highly water soluble drug, metoprolol tartrate (MT) and water insoluble drug nifedipine (NP).

- **Metoprolol Tartrate**

In case of metoprolol, various molecular weight polymers of polyethylene oxide (PEO) were used as a swelling agent and to retard the drug release.

- **Nifedipine**

In order to enhance the solubility of nifedipine, PEG 6000, Mannitol and Poloxamer-188 were explored as solid dispersant. The current study was also focussed on the effect of various molecular weight polymers of PEO 1, 3 and 6 Lac g/mol and the effect of amount of solid dispersing agent for metoprolol and nifedipine respectively.

Monolithic osmotic tablet systems are reported in the patent literature (Liu et al., 2006b; Liu and Wang 2007). The information regarding the effect of tablet formulation variables, orifice size and membrane variables on drug release of this system are less well known. The MOTS controlled-release system, which is composed of a monolithic tablet coated with cellulose acetate membrane with an orifice drilled mechanically, has been described (see Fig 1.9).

When the formulation is administered orally and reaches the stomach, gastric fluid enters inside the core through semipermeable membrane and dissolves the water soluble osmotically active agent (osmogent) and creates osmotic pressure in the core. The drug release occurs through the orifice by osmotic mechanism. The drug release is irrespective of pH and time, and occurs continuously by osmotic mechanism.

Before operation **During operation**

Fig. 1.9 Release mechanism from a Monolithic Osmotic Tablet System (MOTS)

The mechanisms by which drug release is controlled in MOTS are dependent on many variables. One of the principles of drug release would be osmotic pressure. It is possible that one can modulate the release profile of the water soluble, sparingly soluble and poorly soluble active agents by changing the proportion of the hydrophilic polymer (s) in the core and semipermeable polymer in the coating.

CPOP

The aim of the current study was to design a controlled porosity osmotic system (CPOP) based drug delivery system for controlled release of highly water soluble drug, oxybutynin chloride (OC) and sparingly water soluble drug, atenolol (AT).

The current study was also focussed on the effect of concentration of pore formers, Sorbitol, HPMC and PEG-6000.

In case of OC, effects of various ratios of drug to osmogent on the drug release were studied. In order to enhance the solubility of AT, tartaric acid was used as acidifying agent in the core formulation and optimized the quantity.

Controlled porosity osmotic pumps (CPOP), contain water-soluble additives in the coating membrane, which after coming in contact with water, dissolve resulting in an in situ formation of a microporous membrane (see Fig 1.10). The resulting membrane is substantially permeable to both water and dissolved solutes and the mechanism of drug release from these systems was found to be primarily osmotic, with simple diffusion playing a minor role .

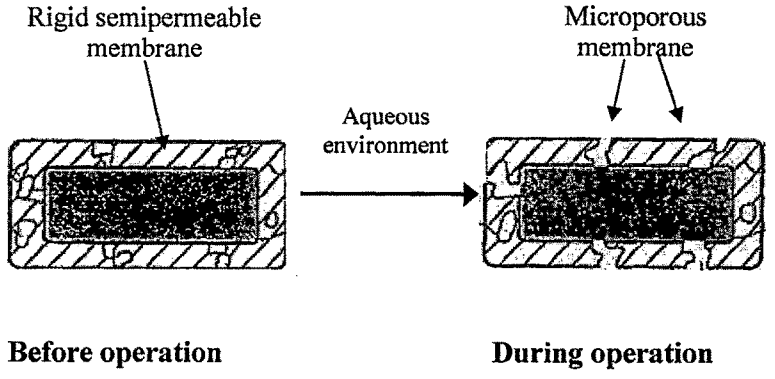

Fig. 1.10 Release mechanism from a Controlled Porosity Osmotic Pump (CPOP)

The mechanisms by which drug release is controlled in CPOP are dependent on many variables. One of the principles of drug release would be osmotic pressure. It is possible that one can modulate the release profile of the water soluble, sparingly soluble and poorly soluble active agents.

PLAN OF WORK

1. Preformulation studies of
    i. Venlafaxine HCl
    ii. Glipizide
    iii. Metoprolol tartrate
    iv. Nifedipine
    v. Oxybutynin chloride
    vi. Atenolol
2. Preparation and characterization of Swellable Porous Osmotic System (SPOP)
    i. Optimization of core and coating components
    ii. *In-vitro* drug release
    iii. Statistical analysis
    iv. Kinetics of drug release
    v. Prediction of *in vivo* performance
3. Monolithic Osmotic Tablet System (MOTS)
    i. Optimization of core, coating components and orifice diameter
    ii. *In-vitro* drug release

iii. Statistical analysis
iv. Kinetics of drug release
v. Prediction of *in vivo* performance

4. Controlled Porosity Osmotic System (CPOP)
   i. Optimization of core and coating components
   ii. *In-vitro* drug release
   iii. Statistical analysis
   iv. Kinetics of drug release
   v. Prediction of *in vivo* performance
5. Performance evaluation of optimized formulations
   i. Effect of pH
   ii. Effect of agitational intensity
   iii. Effect of osmotic pressure
   iv. Scanning electron microscopy
6. *In vivo* studies
7. Stability studies
8. Compilation, analysis and interpretation of results